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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 513/04, 513/14, 491/22, 495/22, 491/14, 471/14, 213/76, 213/84, 495/04 // (C07D 513/04, 285:00, 221:00) (C07D 513/14, 285:00, 221:00, 221:00) (C07D 491/22, 307:00, 243:00, 221:00, 221:00) (C07D 495/22, 333:00, 243:00, 221:00, 221:00) (C07D 491/14, 307:00, 243:00, 221:00)

A1

(11) International Publication Number: **WO 94/17075**

(43) International Publication Date: 4 August 1994 (04.08.94)

(21) International Application Number: PCT/EP94/00102

(22) International Filing Date: 17 January 1994 (17.01.94)

(30) Priority Data:

FI93A000007	20 January 1993 (20.01.93)	IT
FI93A000216	3 November 1993 (03.11.93)	IT

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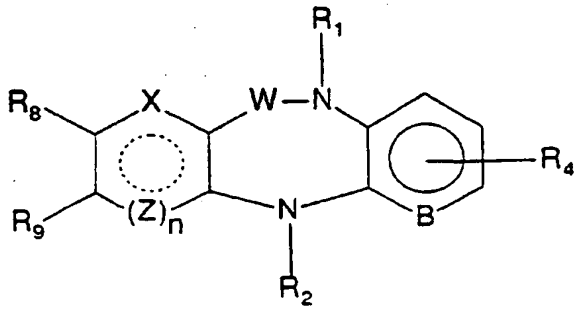
(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: DIAZEPIN DERIVATIVES AND ANTIVIRAL COMPOSITIONS



(I)

(57) Abstract

Described are the diazepin derivatives of general formula (I), their preparation and the antiviral compositions containing them.

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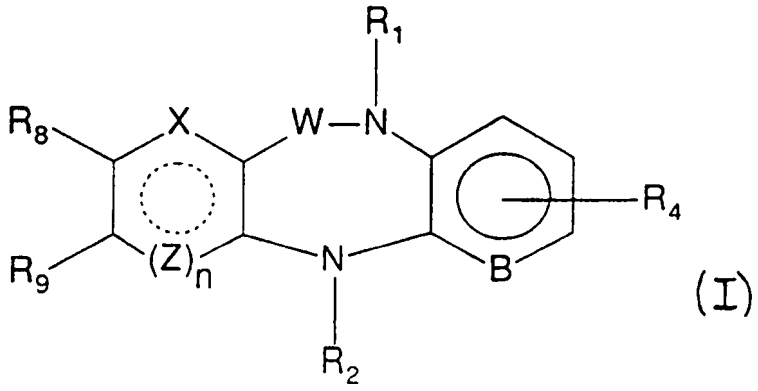
DIAZEPIN DERIVATIVES AND ANTIVIRAL COMPOSITIONS

Field of the invention

The present invention relates to diazepin derivatives suitable for the treatment of viral infections, particularly for the treatment of human infections from HIV, the process for their preparation, the use thereof in pharmaceutical formulations and their pharmaceutically acceptable salts.

Particularly, the present invention relates to diazepin derivatives having the following general formula (I) :



(I)

wherein :

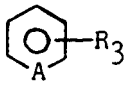
n = 0, 1;

X = =CH, =CR_6, O, S, NR_7;

Z = represents a nitrogen group, optionally substituted with R_2 or with =C-R_5 wherein R_5 is selected from the group consisting of: hydrogen , alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl, hydroxy, amino or acetoamino , nitro , cyano or azido group;

W is selected from the group consisting of: C=O, C=S, SO_2;

R_1 and R_2 equal or different from each other, are selected from the group consisting of hydrogen, alkyl or fluoroalkyl of from 1 to 6 carbon atoms, cycloalkyl of from 3 to 5 carbon atoms, alkenyl or alkinyl of from 3 to 5 carbon atoms, alkoxy-alkyl of from 2 to 6 carbon atoms, benzyl, C_{2-6} alkylacyl, phenylacyl wherein the phenyl group is optionally substituted with a group selected from NO_2, CN, halogen;

R_8, R_9, R_4 and R_6, equal or different from each other, are selected from the group consisting of hydrogen , alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl, hydroxy, amino or acetamino, nitro, cyano and azido group, or R_8 and R_9 linked to each other form a  ring wherein R_3 has the same meaning as

R_4 and A represent a nitrogen atom or $=C-R_5$ wherein R_5 is selected from the group consisting of hydrogen, alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, a halogen, a trihalomethyl, hydroxy, amino or acetamino, a nitro, cyano and azido group;

B has the same meaning as A, but it cannot be equal to $=C-R_5$ when A = $=C-R_5$.

R_7 is selected from the group consisting of H, C_{1-3} alkyl, C_{2-6} alkylacyl, phenylacyl wherein the phenyl group is optionally substituted with a group selected from : NO_2, CN, halogen;

the ring having the substituents R_8 and R_9 can be saturated, unsaturated or partially saturated

provided that :

i) when n = 0, X = O, W = C=O, B = N, R_1 = CH_3, R_4 = H, R_8 and R_9 form a benzenic ring, then R_2 must be different from H;

ii) when n = 1, W =SO_2 and X = CH, then Z and B cannot be contemporaneously equal to CH.

Compounds particularly interesting are those wherein R_2 is alkyl of from 1 to 3 carbon atoms, R_1 and R_4 are hydrogen atoms or alkyl groups containing from 1 to 3 carbon atoms.

The invention also regards the pharmaceutically acceptable salts of general formula (I) with acids, commonly used in the pharmaceutical practice, as for example hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid, mono and bifunctional carboxylic acids as for example acetic acid, propionic acid, maleic acid, succinic acid, fumaric acid, tartaric acid, citric acid.

Prior art

It is known that tricyclic compounds with a heptaatomic diazepinonic ring (EP-A-393604 and EP-A-395229) may have an antiviral activity while tricyclic compounds having heptaatomic thiodiazepin ring (U.S.P. 3.274.058 and 5.011.833) may act on the central nervous system and be myorelaxant agents.

The continuous need to have new drugs for the antiviral therapy has brought to the research and discovery of more and more

substances to be used against viruses.

Detailed description of the invention

It has been unexpectedly found, and this represents an essential characteristic of the present invention that the compounds of general formula (I), as previously defined, show an antiviral action, and are particularly suitable for the treatment of human infections from HIV.

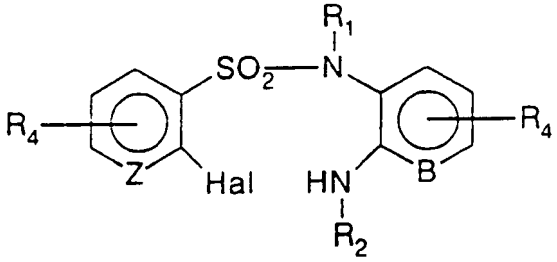
Another essential characteristic of the present invention relates to the pharmaceutically acceptable salts of the compounds of formula (I) with the acids, commonly used in the pharmaceutical practice. Preferred acids are hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid, mono and bifunctional carboxylic acids as for example acetic acid, propionic acid, maleic acid, succinic acid, fumaric acid, tartaric acid, citric acid. A further characteristic of the present invention concerns the pharmaceutical compositions comprising the compounds of general formula (I) and their pharmaceutically acceptable salts and the use of these compounds or salts in the preparation of the above mentioned pharmaceutical compositions.

A further characteristic of the present invention refers to pharmaceutical compositions particularly suitable for parenteral or oral administration.

Another essential characteristic of the present invention consists in the preparation of compounds of general formula (I).

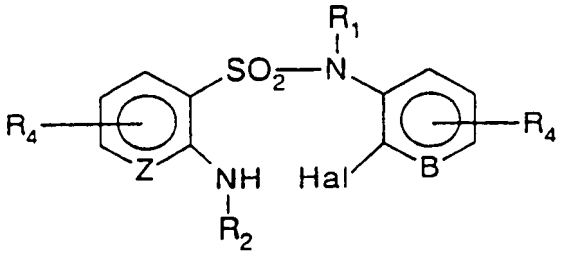
The compounds of general formula (I) as above described wherein n =

1 and W = SO_2 are prepared through the cyclization of sulfonamides of general formula (II)



(II)

or sulfonamides of general formula (III)



(III)

wherein R_4, R_5, Z and B have been previously defined for the compounds of formula (I); R_1 and R_2 have the same meanings of the corresponding substituents of the compounds of formula (I) or represent a protecting group as for example acetyl, benzoyl, benzyl, Hal represents a halogen atom, preferably chlorine or bromine. The cyclization reaction is carried out in an organic solvent, preferably in the presence of a base and optionally can be used copper or its salts in a catalytic amount. The preferred organic solvents are dimethylformamide, dioxane, tetrahydrofuran, dimethylsulfoxide and alcohols, while the preferred bases are the

alkaline carbonates, preferably potassium carbonate and alkaline hydrides, preferably sodium hydride.

The reaction mixture is preferably heated up to temperatures comprised between 60 ° - 200 °C.

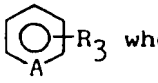
The compounds of general formula (I) wherein R_1 and R_2 are different from hydrogen can be obtained by means of a reaction carried out in a single step, that is by treating in situ salts of the compounds of general formula (I) wherein R_1 and R_2, also individually are hydrogen with a R'Q compound wherein R' is selected from the group consisting of alkyl or fluoroalkyl of from 1 to 6 carbon atoms, cycloalkyl of from 3 to 5 carbon atoms, alkenyl or alkynyl of from 3 to 5 carbon atoms and wherein Q is a suitable leaving group as for example a halogen, preferably chlorine, bromine or iodine, or an appropriate aliphatic or aromatic ester of the sulphonic acid.

These salts can be obtained by treating the compounds of general formula (I) in case R_1 and/or R_2 = hydrogen with organic bases as alkaline metal hydrides, for example sodium hydride, with alkyl lithium, as for example n-butyl lithium, amides of alkaline metals, as for example sodium amide or lithium dialkylamides, as for example lithium diisopropylamides; R'Q is added to the suspension of the salt in inert organic solvents, preferably dioxane, tetrahydrofuran and dimethylformamide, at a temperature comprised between the room and the reflux temperature of the reaction mixture, thereby obtaining the desired derivatives.

In case R_1 and R_2 are hydrogen and these two atoms are to be substituted, two moles of base and two moles of R'Q shall be used, whereas, in case only the substitution on the sulphamidic nitrogen atom is requested, a mole of base and a mole of R'Q shall be added.

Starting from the compounds having R_2 equal to hydrogen and R_1 a protecting group, as for example arylmethyl or arylacyl group, the treatment with R'Q leads to the substitution of the nitrogen aminic group and the subsequent deprotection gives the products of general formula (I) wherein R_2 has the above defined meanings , with the exception of the meaning R_2 = hydrogen, and R_1 is equal to hydrogen.

The sulfonamides of general formula (II) and (III) are prepared by already known methods, used for analogous derivatives (D. Giannotti, et. al. J. Med. Chem. 1991, 34, 1356-1362).

The compounds of general formula (I) wherein n = 0, W = C=O or C=S, X=O, S or NR_7, R_8 and R_9 form a ring  wherein A represent a nitrogen atom or a $=C-R_5$ group (wherein R_7, R_3 and R_5 are defined as above), can be synthetized according to the herewith submitted Scheme 1.

This synthetic method is an extension of that described by G.Viti et al. in J.Het. Chem. 27,1369 (1990) for arylbenzofurandiazepin-6-ones.

As can be seen from scheme 1a, the synthesis is realized in various steps :

a) by condensation of the compounds of formula (IV), wherein X R_3 and A have the above mentioned meanings in the form of sodium or potassium salts, with the compounds of formula (V), wherein Hal, B and R_4 have the above mentioned meanings, in the presence of polar solvents and at a temperature comprised between the room and the reflux temperature, the compounds of formula (VI) are obtained (see also example 6).

In some cases, the compounds of formula (VI) are not isolated because the condensation reaction proceedes up to the formation of the compounds of formula (VII) or (VIII), (see example 11 and 12). In all these compounds R_1, R_2, R_3, R_4 R_5, A, B, X have the same meanings as in the compounds of formula (I), Hal is halogen (preferably chlorine and bromine).

b) The compounds of formula (VI) and formula (VII) are cyclized to the compounds of general formula (I) wherein R_2 is equal to hydrogen and W = C=O and represented in the scheme as compounds of formula (VIII). The cyclization reaction is carried out in an organic solvent in the presence of a base and optionally of copper or its salts in a catalytic amount. The preferred organic solvents are dimethylformamide, dioxane, dimethylsulfoxide, pyridine and alcohols, while the preferred bases are the alkaline carbonates, preferably potassium or sodium carbonate and alkaline hydrides, preferably sodium hydride.

The reaction mixture is preferably heated up to temperatures

comprised between 60 ° - 200 °C.

These cyclization reactions are described in example 7.

When this reaction is carried out with the compounds of formula (VI) or (VII) wherein R_1 represents a protecting group, this group can be removed by hydrolytic methods, for example with a strong acid, such as trifluoroacetic acid at a temperature comprised between -10 °C and 100 °C, thereby obtaining the compounds of general formula (I) wherein R_1 is equal to H.

c) Starting from the compounds of formula (VIII), the compounds of general formula (I) can be obtained, wherein R_1 and R_2 are different from H and W = C=O, represented in the scheme as compounds of formula (IX), by means of a one step reaction , by treating in situ the compounds of formula (VIII) with a R_2M compound wherein R_2 has the above defined meaining and M is a suitable leaving group, as for example chlorine, bromine, iodine or a suitable aliphatic or aromatic ester of the sulfonic acid.

These salts can be obtained by treating compounds of general formula (VIII) with inorganic bases such as alkaline metals hydrides, for example sodium hydride, with alkyl lithium, as for example n-butyl lithium, amides of alkaline metals as for example sodium amide, or lithium dialkyl amides as for example lithium diisopropylamide; R_2M is added to the salt suspension in inert organic solvents, preferably dioxane, tetrahydrofuran and dimethylformamide, at a temperature comprised between the room and the reflux temperature, thus obtaining the desired compounds.

These alkylation reactions are described in example 8.

In case two hydrogen atoms are to be substituted in the compounds of formula (VIII), wherein R_1 is represented by hydrogen, or X = NH, two moles of base and two moles of R_2M shall be used (see example 13); starting from the compounds wherein R_1 is a protecting group, for example an arylmethyl, arylacyl group, the treatment with R_2M brings to the substitution of the aminic nitrogen and the subsequent deprotection gives the compounds of general formula (I) wherein R_2 has the above mentioned meanings, with the exception of the meaning R_2 = H, and R_1 = H.

d) The compounds of formula (X), corresponding to the compounds of general formula (I) wherein W = C=S, are obtained by reacting compounds of formula (IX) with a sulfuring reactive as for example 2,4-bis(4-methoxyphenyl) 1,3-dithio-2,4-diphosphetan-2,4-disulphide (Lawesson reactant), bis-(trimethylsilyl) sulphide or phosphorus pentasulphide.

The reaction is carried out in an organic solvent as for example benzene or toluene at a temperature comprised between the room and the reflux temperature.

This reaction is described in example 9.

The invention relates also to products obtained by the reduction of the double bond joining the pentaatomic ring with the heptaatomic ring. The compounds of formula (XI) are obtained by reducing the compounds of formula (IX) with hydrogen at a pressure

ranging from 1 to 10 atm, in the presence of a catalyst as for example 10 % Pd/C or Nickel-Raney (as described in example 10).

Also in this case, from the compounds of formula (XI) the corresponding thiolamides of general formula (XII) can be obtained by using the same procedures described for the synthesis of the compounds of formula (X).

The compounds of general formula (I), prepared as described above, in combination with inorganic and organic acids commonly used in the pharmaceutical practice, preferably hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid, mono and bifunctional carboxylic acid, preferably acetic acid, propionic acid, maleic acid, succinic acid, fumaric acid, tartaric acid, citric acid are used in the preparation of pharmaceutically acceptable salts.

A therapeutically effective dose of the compound of general formula (I) or of its pharmaceutically acceptable salts, prepared as above described, is used as active principle in combination with suitable excipients and diluents, in the preparation of pharmaceutically acceptable compositions.

A therapeutically effective dose of the compound of general formula (I) is further used in combination with suitable excipients, in the preparation of pharmaceutical compositions particularly suitable for parenteral and oral administration. The compounds of general formula (I) show antiviral activity, particularly against HIV-1 virus in human infections.

The antiviral activity evaluation is carried out by using :

a) lynphoblastoid cellular line CD4+ known as C8166 containing HTLV-I genoma expressing only "TAX" gene which is infected by HIV-1 (strain 3B);

b) mononucleated cells of human blood (PBMC) infected by HIV-1 virus of the P1 strain which is the viral isolation obtained by the patient affected by AIDS.

The evaluation of the viral inhibition is carried out with the methods described in literature by :

1) Dianzani F., Antonelli G., Capobianchi M.R., De Marco F. (1988) "Replication of Human Immunodeficiency Virus Yield of Infectious Virus Under Single Growth Cycle Conditions", Arch. Virol. 103, 127-131;

2) Dianzani F., Capobianchi M.R., Antonelli G., Amicucci P., De Marco F. "Susceptibility of Human Immunodeficiency Virus to Antiviral Agents Measured by Infectious Virus Yield Reduction", Antiviral Res. 11(1989), 299-306. The above mentioned publications 1) and 2) define also the terminology used at the previous points a) and b).

Cellular cytotoxicity is evaluated by using methyl-tetrazole bromide (MTB) according to the method described by Pauwels R., Balzarini J., Baba M., Snoeck R., Schols D., Herdewijn P., Desmeyter J., De Clercq E., (1988) "Rapid and Automated Tetrazolium-Based Colorimetric Assay for the Detection of Anti-HIV Compounds", J. Virol. Methods 20, 309-321.

Some representative examples of the compounds of the present invention and the relative synthesis processes are reported hereinbelow.

EXAMPLE 1

N-methyl-N-(2-acetylamino-pyridin-3-yl)-(2-chloro-pyridin-3-yl) sulfonamide [compound of general formula (II) wherein : Hal = Cl; $R_1 = CH_3$; $R_2 = COCH_3$; $R_3 = R_4 = H$, Z = B = N].

3.4 g (16 mmoles) of (2-chloropyridin-3-yl)thiochloride dissolved in 40 ml tetrahydrofuran are added to 2.4 g (16 mmoles) of 3-amino-2-acetylamino-pyridine dissolved in 12 ml pyridine.

The mixture is kept for one hour under stirring at room temperature and then it is dried. The residue is treated with 5 ml water and the obtained crystalline solid is filtered and dried, obtained are 2.6 g (8 mmoles) of N-(2-acetylamino-pyridin-3-yl)-(2-chloro-pyridin-3-yl) sulphonamide (m.p.: 188 ° - 190 °C (water)).

The product is solubilized in 20 ml of a methanol solution containing 0.184 g (8 mmoles) of sodium, then 1 ml of methyl hydride is added, the resulting mixture is kept two days under rest, brought to dryness, solubilized in ethyl acetate, washed with water, dried and concentrated obtaining 1.9 g of a white crystalline solid. Yield 35 %, m.p.: 145 - 146 °C.

EXAMPLE 2

5-methyl-5,11-dihydro-pyrido[3,2-c][1,2,5] benzothiodiazepin-6,6-dioxide [compound of general formula (I) wherein : n = 1; Z = =CH; X = =CH; $R_1 = CH_3$; $R_2 = R_4 = R_8 = R_9 = H$; $W = SO_2$; B = N].

5 g of potassium carbonate are added to 11 g of N-methyl-N(2-chloro-pyridin-3-yl)-2-amino-benzensulphonamide dissolved in 100 ml of dimethylformamide. The reaction mixture is heated for 8 hours under reflux, then it is cooled and poured into water thus obtaining a precipitate that is filtered and dried.

Melting point 202 - 204 °C (95 °C ethanol); yield 72%.

EXAMPLE 3

6,8,9-trimethyl-6,11-dihydro-pyrido [2,3-f] [2,1,5]-benzothio-diazepin-5,5-dioxide [general formula (I) wherein : n = 1; W = SO_2; Z = N; X = =CH; B = = CH; R_1 = CH_3; R_2 = H; R_4 = 8-CH_3, 9-CH_3; R_8 = R_9 = H].

4 g of iron reduced by hydrogen are added in small doses to a 4.3 g (0.013 moles) solution of N-methyl-N(2-nitro-4,5-dimethylphenyl)-(2-chloro-pyridin-3-yl) sulfonamide dissolved in 70 ml acetic acid, heated to the reflux temperature. The mixture is maintained under reflux for 1 hour, then when it is still hot, is filtered and the filtrate is poured into icy water. The crystallized solid obtained is filtered, washed with water and dried.

3 g of product are obtained, yield 87 %. m.p.: 211 - 212 °C.

EXAMPLE 4

6-methyl-6, 11-dihydro-dipyrido[3,2-c:2',3'-f][1,2,5]-thiodiazepin -5,5-dioxide [general formula (I) wherein : n = 1; W = SO_2;Z = N; X= = CH; B = N; R_1 = CH_3; R_2 = R_4 = R_8 = R_9 = H].

0.5 g (3.6 mmoles) of potassium carbonate, 0.3 g copper, 0.3 g

cuprous bromide are added to 2.3 g (6.7 mmoles) N-methyl-N(2-acetylamino-pyridin-3-yl)-(2-chloro-pyridin-3-yl) sulfonamide dissolved in 40 ml dimethylformamide. The obtained mixture is maintained under reflux for 2 hours and after cooling is poured into water and extracted with dichloromethane. The organic phase, is washed with water, anhydrified and concentrated to dryness. The residue is purified by chromatography on SiO_2 column using as the eluant ethyl ether.

1.35 g of product are obtained with a yield of 77 %. Melting point: 202 - 203 °C.

9-chloro-5, 8-dimethyl-5,11-dihydro-pyrido[3,2-c][1,2,5]-benzothio-diazepin-6,6-dioxide is prepared by operating as above described. Melting point 253-254 °C (methanol); yield 83%.

EXAMPLE 5

11-ethyl-6, 8, 9-trimethyl-6,11-dihydro-pyrido[2,3-f][2,1,5] benzo-thiodiazepin-5,5-dioxide [general formula (I) wherein : n = 1; W = SO_2; $R_1 = CH_3$; $R_2 = C_2H_5$; R_4 = 8-CH_3, 9-CH_3; Z = N; B= = CH; X = CH; $R_8 = R_9$ = H].

170 mg (5.5 mmoles) 80% NaH are added to 1.4 g (5 mmoles) 6,8,9-trimethyl-6,11-dihydro-pyrido[2,3-f][2,1,5]benzothiodiazepin-5,5-dioxide dissolved in 10 ml dimethylformamide and after maintaining the mixture for 30 minutes at room temperature and 30 minutes at 60 °C, 7.5 mmoles ethyl iodide are added. The mixture is maintained for 3 hours under stirring and one night under rest and then is poured into a saturated aqueous solution of sodium chloride and

extracted with ethyl ether. The ethereal extract is washed with water, anhydrified and concentrated to dryness.

The solid product is purified by chromatography on SiO_2 column by using as the eluant ethyl ether/hexane 1/1, collecting 1.1 g of product, yield 70%. Melting point 149 - 150 °C.

By operating as above described the following products are also prepared:

11-ethyl-5-methyl-5,11-dihydro-pyrido[3,2-c][1,2,5]-benzothiodiazepin-6,6-dioxide (Yield 60%; m.p.: 158-159°C) 11-ethyl-6-methyl-6,11-dihydro-dipyrido[3,2-c:2',3'-f][1,2,5]-thiadiazepin-5,5-dioxide (Yield 72%, m.p.: 122-123 °C).

11-isopropyl-6,8,9-trimethyl-6,11-dihydro-pyrido[2,3-f][2,1,5] benzothiodiazepin-5,5-dioxide (Yield 40 %; m.p.: 138 - 140 °C).

9-chloro-5,8-dimethyl-11-ethyl-5,11-dihydro-pyrido[3,2-c] [1,2,5]benzothiodiazepin-6,6-dioxide (Yield 23.8%, m.p.: 147 °C).

1-isopropyl-6,8,9-trimethyl-1,6-dihydro-pyrido[2,3-f][2,1,5] benzothiodiazepin-5,5-dioxide.

1-ethyl-6,8,9-trimethyl-1,6-dihydro-pyrido[2,3-f][2,1,5]benzothiodiazepin-5,5-dioxide m.p.= 149-150°C.

EXAMPLE 6

N-(2-chloropyridin-3-yl)-2-[(cyanopyridin-3-yl)oxy]acetamide [general formula (VI) wherein : R_1 is H; R_3 and R_4 are H; X is O, A and B are N, Hal is Cl].

3.3 g 2-cyano-3-hydroxypyridine are added to 0.7 g of sodium

dissolved in 100 ml n-propanol, then after maintaining for 30 minutes under stirring, 6.9 g of 2-chloro-3-bromoacetylamino-pyridine are added and the mixture is heated for 8 hours under reflux.

The reaction mixture is poured into icy water and the solid precipitate formed is filtered, washed with water and dried; the product is purified by washing with hot acetone, 3.5 g are obtained, yield 44 %; m.p. = 220 °C (it decomposes).

EXAMPLE 7

12-H-6,7-dihydro-7-methyl-pyrido[2,3-b]pyrido-[2',3'-4,5]-furo-[2,3-f]-[1,4]diazepin-6-one [general formula (I) wherein : n = 0; R_1 is CH_3; R_2 and R_4 are H; X = O; B = N; W = C=O; R_8 and R_9 form together the ring ].

0.39 g (2.8 mmoles) potassium carbonate are added to 1.7 g (5.6 mmoles) N-methyl-N-(2-chloropyridin-3-yl)-2-[(2-cyanopyridin-3-yl)oxy]acetamide dissolved in 50 ml N,N-dimethylformamide. The reaction mixture is maintained under reflux for 12 hours, brought to dryness, treated with water, filtered and dried; 1.4 g of product are obtained, yield 94%, m.p. = 183 °C (decomposes) (95 ° ethanol).

By operating as above described the following products of general formula (I) are obtained:

12-H-6,7-dihydro-7-benzyl-pyrido[2,3-b]pyrido[2',3'-4,5] furo [2,3-f]-[1,4] diazepin-6-one (Yield 58%, m.p.: 194-195 °C).

12-H-6,7-dihydro-7-ethyloxymethyl-pyrido[2,3-b] pyrido [2',3'-4,5] furo [2,3-f]-[1,4] diazepin-6-one (Yield 50 %).

^{1}H-NMR (d, $CDCl_3$) : 1.20 (t, 3H), 3.76 (q, 2H), 5.08 (s, 2H), 7.00 (dd, 1H), 7.32 (dd, 1H), 7.72 (d, 1H), 7.92(d, 1H), 8.00 (s, 1H), 8.07 (d, 1H), 5.51 (d, 1H).

12-H-6,7-dihydro-pyrido [2,3-b] pyrido [2',3'-4,5] thien [2,3-f] [1,4] diazepin-6-one (Yield 64 %; m.p.: 247 °C (decomposes)).

12-H-6,7-dihydro-7-methyl-pyrido [2,3-b] pyrido [2',3'-4,5] thien [2,3-f] [1,4] diazepin-6-one (Yield 89 %); m.p.: 230 - 231 °C).

12-H-6,7-dihydro-7,8-dimethyl-pyrido [2,3-b] pyrido [2',3'-4,5] furo [2,3-f] [1,4] diazepin-6-one (Yield 32 %; m.p.: 280 - 282 °C (ethanol)).

EXAMPLE 8

12-H-6,7-dihydro-7-methyl-12-ethyl-pyrido [2,3-b] pyrido [2',3'-4,5] furo [2,3-f] [1,4] diazepin-6-one [general formula (I) wherein: n = 0; R_1 = CH_3; R_2 = C_2H_5; R_4 = H; X = O; B = N; W = C = O; R_8 and R_9 form together the ring ].

0.7 of 80% sodium iodide are added under stirring to 1.2 g (4.5 mmoles) 12-H-6,7-dihydro-7-methyl-pyrido-[2,3-b] pyrido-[2',3'-4,5] furo [2,3-f]-[1,4] diazepin-6-one dissolved in 30 ml N,N-dimethylformamide. After 1 hour the mixture is treated with 1 ml ethyl iodide and maintained under stirring for 4 hours and under rest for 2 days, then poured into icy water, thus obtaining a solid precipitate which is filtered, washed with water, dried and

purified on (SiO_2) flash column, eluant : ethyl acetate.

0.9 g of product are obtained, yield 68 %, m.p. = 138 °C.

By operating as above described the following products of general formula (I) are obtained :

12-H-6,7-dihydro-7-methyl-12-ethyloxymethyl-pyrido [2,3-b] pyrido [2', 3'-4,5] furo [2,3-f] [1,4] diazepin-6-one (Yield 12 %; m.p. = 143 - 145 °C).

12-H-6,7-dihydro-7-benzyl-12-ethyl-pyrido [2,3-b] pyrido [2',3'-4,5] furo [2,3-f] [1,4] diazepin-6-one (Yield 74 %; m.p. = 145 °C (it decomposes)).

12-H-6,7-dihydro-7-ethyloxymethyl-12-ethyl-pyrido [2,3-b] pyrido-[2',3'-4,5] furo [2,3-f] [1,4] diazepin-6-one (Yield 53 %).

^{1}H-NMR (d, $CDCl_3$) : 1.20(t, 3H), 1.34(t, 3H), 3.75(q, 2H), 4.82(q, 2H), 5.17(s, 2H), 7.06(dd, 1H), 7.30(dd, 1H), 7.80(m, 2H), 8.16(d, 1H), 8.55(d, 1H);

12-H-6,7-dihydro-7-methyl-12-ethyl-pyrido [2,3-b] pyrido [2',3'-4,5] thien [2,3-f] [1,4] diazepin-6-one (Yield 83 %; m.p. = 174 - 176 °C);

12-H-6,7-dihydro-7,8-dimethyl-12-ethyl-pyrido [2,3-b] pyrido [2',3'-4,5] furo [2,3-f] [1,4] diazepin-6-one (Yield 80 %; m.p. = 176 - 177 °C).

12-H-5,6-dihydro-5-methyl-12-ethyl-benzofuro[3,2-b]pyrido[3,2-f] diazepin-6-one, yield 55%, m.p. 157-158°C;

12-H-6,7-dihydro-7-methyl-12-isopropyl-pyrido[2,3-b]-pyrido-[2',3'-4,5]furo[2,3-f][1,4]diazepin-6-one;

12-H-6,7 dihydro-7-methyl-12-isopropyl-pyrido[2,3-b]pyrido[2',3'-4,5]thien[2,3-f][1,4]diazepin-6-one.

EXAMPLE 9

12-H-6,7-dihydro-7-methyl-12-ethyl-pyrido [2,3-b] pyrido-[2',3'-4,5] furo [2,3-f] [1,4] diazepin-6-thione [general formula (I) wherein : n = O; R_1 = CH_3; R_2 = C_2H_5; R_4 = H; X = O; B = N; W = C = S; R_8 and R_9 form together the ring ].

140 mg Lawesson reactant are added to 0.2 g 12-H-6,7-dihydro-7-methyl-12-ethyl-pyrido-[2,3-b] pyrido-[2',3'-4,5] furo [2,3-f]-[1,4] diazepin-6-one dissolved in 15 ml toluene. The obtained mixture is maintained under reflux for 2 hours, then after cooling it is brought to dryness and the solid residue is purified by chromatography on SiO_2 flash column, eluant : cyclohexane/ethyl acetate 6/1.

0.18 g of product are obtained, yield 85 %, m.p. = 217 - 218 °C.

By operating as above described the following product is obtained : 12-H-6,7-dihydro-7-methyl-12-ethyl-pyrido [2,3-b] pyrido [2',3'-4,5] thien [2,3-f] [1,4] diazepin-6-thione (Yield 67 %; m.p.: 163 - 165 °C).

12-H-6,7-dihydro-7-methyl-12-isopropyl-pyrido-[2,3-b]-pyrido-[2',3'-4,5]furo[2,3-f][1,4]diazepin-6-thione;

12-H-6,7-dihydro-7-methyl-12-isopropyl-pyrido-[2,3-b]pyrido[2',3'-4,5]thien[2,3-f][1,4]diazepin-6-thione.

EXAMPLE 10

12-H-7-methyl-12-ethyl-5a,6,7,12a-tetrahydro-pyrido [2,3-b] pyrido [2',3'-4,5] furo [2,3-f] [1,4] diazepin-6-one (5a, 12a cis) [general formula (I) in reduced form wherein : n = 0; R_1 = CH_3; R_2 = C_2H_5; R_4 = H; X = O; B = N; W = C = O; R_8 and R_9 form together the ring ].

100 mg 12-H-6,7-dihydro-7-methyl-12-ethyl-pyrido-[2,3-b] pirido-[2',3'-4,5] furo [2,3-f]-[1,4] diazepin-6-one dissolved in 10 ml glacial acetic acid is hydrogenated for 6 hours at 45 psi pressure and at room temperature in the presence of 20 mg Pd/C (10 %). The mixture is filtered and brought to dryness. The residue is treated with a sodium carbonate solution, extracted with ethyl acetate, anhydrified and brought to dryness; the obtained product is purified by SiO_2 flash column chromatography, eluant : ethyl acetate; yield 21 %, m.p. = 184 - 186 °C.

By operating as above described the following product is obtained : 12-H-7-benzyl-12-ethyl-5a,6,7,12a-tetrahydro-pyrido [2,3-b] pyrido [2',3'-4,5] furo [2,3-f] [1,4] diazepin-6-one (5a,12a cis) (Yield 15 %).

^{1}H-NMR (d, $CDCl_3$) : 0.98(t, 3H), 3.30(dq, 1H), 3.85(dq, 1H), 4.82(d, 1H), 5.39(d, 1H), 5.25(s, 2H), 6.76(d, 1H), 6.83(dd, 1H), 6.96(dd, 2H), 7.23(m, 5H), 7.43(d, 1H), 7.80(d, 1H), 8.14(d, 1H).

EXAMPLE 11

N-(2-chloro-pyridin-3-yl)-3-amino-2-thien [3,2-b]-pyridin-carboxy-amide [general formula (VII) wherein : R_1 = H; R_3 and R_4 = H; X =

S; A = B = N; Hal = Cl].

0.5 g (3.6 mmoles) 3-mercapto-2-cyan-pyridine and 900 mg (3.6 mmoles) 2-chloro-3-bromoacetylaminopyridine are added to 85 mg (3.6 mmoles) sodium dissolved in 20 ml methanol. The mixture in maintained for 4 hours under stirring, then the precipitate is filtered, washed with methanol and with water and finally brought to dryness.

Obtained are 992 mg of final product, yield 90 %, m.p. = 224 - 225 °C (95° ethanol).

N-(2-chloro-pyridin-3-yl)-N-methyl-3-amino-2-thien[3,2-b]-pyridin-carboxylamide is obtained by operating as above described. (Yield 81 %; m.p. = 202 - 203 °C).

EXAMPLE 12

12-H-5,6-dihydro-5-methyl-indole [3,2-b] pyrido [3,2-f] [1,5] diazepin-6-one [general formula (I) wherein : n = 0; R_1 = CH_3; R_2 = R_4 = H; X = NH; W = C = O; B = N; R_8 and R_9 form together a benzenic ring].

600 mg (18 mmoles) 80 % NaH are added under stirring to 3 g (18 mmoles) 2-acetylaminobenzonitrile dissolved in 50 ml N,N-dimethylformamide.

After 1 hour, 4.4 g (18 mmoles) 2-chloro-3-bromoacetyl-aminomethyl-pyridine dissolved in 10 ml N,N-dimethylformamide are added drop by drop and the mixture in maintained 8 hours under stirring, then 1 g of potassium carbonate is added.

The mixture is kept 12 hours under reflux, then it is poured into water and the precipitate is recovered. By extraction with ethanol a solid product is obtained, (yield 20 %), m.p. 208 - 210 °C (ethyl acetate), while a part which is insoluble is formed by :

12-H-5,6-dihydro-5-methyl-12-acetyl-indole [3,2-b] pyrido [3,2-f] [1,5] diazepin-6-one (Yield 13 %; m.p.: 304 - 306 °C (it decomposes)).

By operating as above described the following products are prepared:

12-H-5,6-dihydro-10-chloro-5-methyl-indole [3,2-b] pyrido [3,2-f] [1,5] diazepin-6-one (Yield 22 %; m.p.: 164 - 165 °C (95° ethanol));

12-H-5,6-dihydro-12-acetyl-10-chloro-5-methyl-indole [3,2-b] pyrido [3,2-f] [1,5] diazepin-6-one (Yield 20 %; m.p.: 270 °C (it decomposes)).

EXAMPLE 13

12-H-5,6-dihydro-5-methyl-7,12-diethyl-indole [3,2-b] pyrido [3,2-f] [1,5] diazepin-6-one [general formula (I) wherein : n = 0; R_1 = CH_3; R_2 = C_2H_5; R_4 = H; X = NC_2H_5; B = N; W = C = O; R_8 and R_9 form together a benzenic ring].

55 mg (1.5 mmoles) 80 % NaH are added under stirring to 122 mg (0.46 mmoles) 12-H-5,6-dihydro-5-methyl-indole [3,2-b] pyrido [3,2-f] [1,5] diazepin-6-one dissolved in 4 ml dimethylformamide.

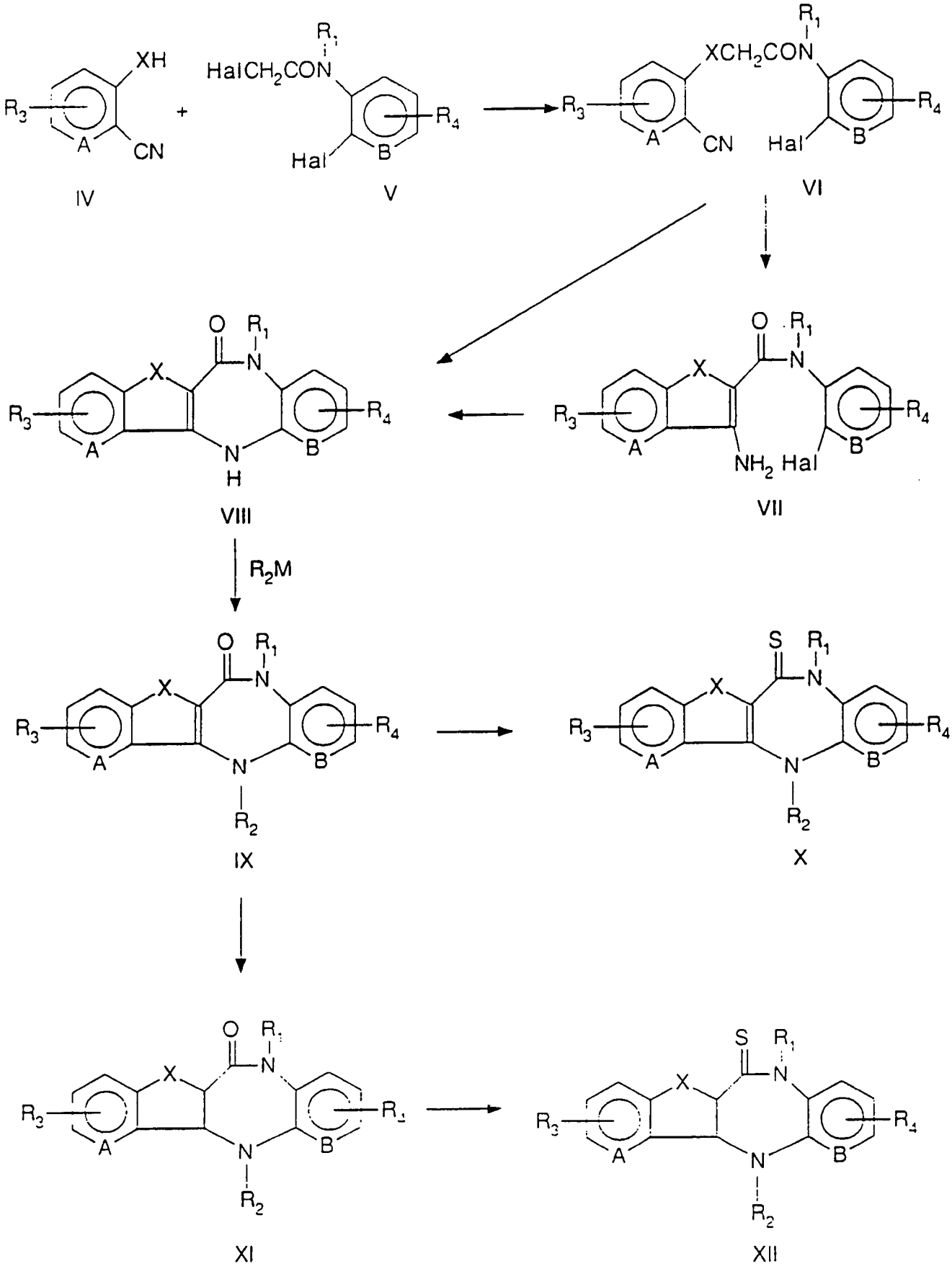
After 1 hour the mixture is treated with 0.2 ml ethyl iodide and stirred for 4 hours. After one night under rest, it is poured into cold water, extracted with dichloro methane, dried and the solvent

is evaporated. The residue is purified on SiO_2 flash column, eluant cyclohexane/ethyl acetate 4/1. Obtained are 22 mg (Yield 15 %). ^{1}H-NMR (d, $CDCl_3$): 1.38 (m, 6H), 3.47 (s, 3H), 4.15 - 4.55(m, 4H), 7.02(m, 2H), 7.20-7.45(m, 3H), 7.86(d, 1H), 8.1(d, 1H).

By operating as above described the following compounds of formula (I) are prepared:

12-H-5,6-dihydro-7-ethyl-5-methyl-10-chloro-indole [3,2-b] pyrido [3,2-f] [1,5] diazepin-6-one;

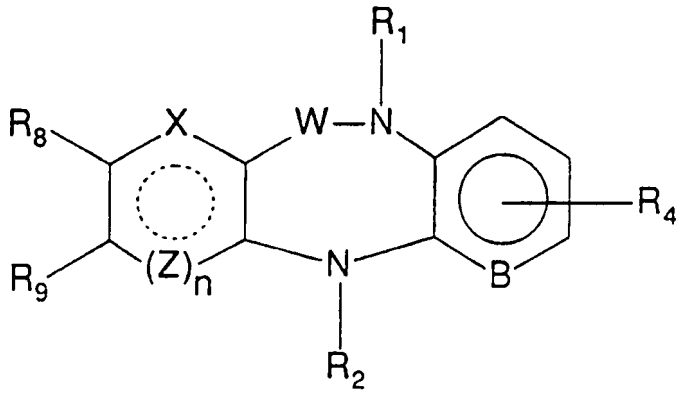
12-H-5,6-dihydro-1,2,8,9-ethyl-5-methyl-10-chloro-indole [3,2-b] pyrido [3,2-f] [1,5] diazepin-6-one.



Scheme 1

CLAIMS

1. Tetracyclic diazepin compounds having the following general formula (I) :



(I)

wherein :

n = 0, 1;

X = =CH, $=CR_6$, O, S, NR_7;

Z = represents a nitrogen group, optionally substituted with R_2 group; or with $=C-R_5$ wherein R_5 is selected from the group consisting of hydrogen , alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl, hydroxy, amino or acetamino , nitro , cyano or azido group;

W is selected from the group consisting of C=O, C=S, SO_2;

R_1 and R_2 equal or different from each other, are selected from the group consisting of hydrogen, alkyl or fluoroalkyl of from 1 to 6 carbon atoms, cycloalkyl of from 3 to 5 carbon atoms, alkenyl or an alkinyl of from 3 to 5 carbon atoms, an alkoxy-alkyl of from 2 to 6 carbon atoms, benzyl, C_{2-6} alkylacyl, phenylacyl wherein the

phenyl group is optionally substituted with a group selected from NO_2, CN, halogen;

R_8, R_9, R_4 and R_6, equal or different from each other, are selected from the group consisting of hydrogen, alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl , hydroxy , amino or acetamino, nitro, cyano and azido group, or R_8 and R_9 linked to each other form a  ring wherein R_3 has the same meaning as R_4

and A represents a nitrogen atom or $=C-R_5$, wherein R_5 is selected from the group consisting of hydrogen , alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl , hydroxy amino or acetamino group, nitro, cyano and azido group;

B has the same meaning as A, but it cannot be equal to $=C-R_5$ when A = $=C-R_5$.

R_7 is selected from the group consisting of H, C_{1-3} alkyl, C_{2-6} alkylacyl, phenylacyl wherein the phenyl group is optionally substituted with a group selected from : NO_2, CN, halogen;

the ring having the substituents R_8 and R_9 can be saturated, unsaturated or partially saturated

provided that :

i) when n = 0, X = O, W = C=O, B = N, R_1 = CH_3, R_4 = H, R_8 and R_9 form a benzenic ring, then R_2 must be different from H;

ii) when n = 1, W = SO_2 and X = CH, then Z and B cannot be

contemporaneously equal to CH.

2. The compounds of general formula (I) as claimed in claim 1, wherein : R_2 is an alkyl of from 1 to 3 carbon atoms, R_1 and R_4 are hydrogen atoms or alkyl groups of from 1 to 3 carbon atoms.

3. The compounds as claimed in claim 1 represented by :

5-methyl-5,11-pyrido[3,2-c][1,2,5]benzothiodiazepin-6,6-dioxide;

9-chloro-5,8-dimethyl-5,11-dihydro-pyrido[3,2-c][1,2,5]-benzothiodiazepin-6,6-dioxide;

6,8,9-trimethyl-6,11-dihydro-pyrido[2,3-f][2,1,5]-benzothiodiazepin-5,5-dioxide;

6-methyl-6,11-dihydro-dipyrido[3,2-c:2',3'-f][1,2,5]-thiodiazepin-5,5-dioxide;

11-ethyl-6,8,9-trimethyl-6,11-dihydro-pyrido[2,3-f][2,1,5] benzothiodiazepin-5,5-dioxide;

11-ethyl-5-methyl-5,11-dihydro-pyrido[3,2-c][1,2,5]-benzothiodiazepin-6,6-dioxide;

11-ethyl-6-methyl-6,11-dihydro-dipyrido[3,2-c:2',3'-f][1,2,5]-thiadiazepin-5,5-dioxide;

11-isopropyl-6,8,9-trimethyl-6,11-dihydro-pyrido[2,3-f][2,1,5] benzothiodiazepin-5,5-dioxide;

9-chloro-5,8-dimethyl-11-ethyl-5,11-dihydro-pyrido[3,2-c][1,2,5] benzothiodiazepin-6,6-dioxide;

1-isopropyl-6,8,9-trimethyl-1,6-dihydro-pyrido[2,3-f][2,1,5] benzothiodiazepin-5,5-dioxide;

12-H-6,7-dihydro-7-methyl-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7-benzyl-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7-ethyloxymethyl-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-pyrido[2,3-b]pyrido[2',3'-4,5]thien[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7-methyl-pyrido[2,3-b]pyrido[2',3'-4,5]thien[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7,8-dimethyl-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7-methyl-12-ethyl-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7-methyl-12-ethyloxymethyl-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7-benzyl-12-ethyl-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7-ethyloxymethyl-12-ethyl-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7-methyl-12-ethyl-pyrido[2,3-b]pyrido-[2',3'-4,5]thien[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7,8-dimethyl-12-ethyl-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one;

12-H-6,7-dihydro-7-methyl-12-ethyl-pyrido[2,3-b]pyrido-[2',3'-4,5]

furo[2,3-f]-[1,4]diazepin-6-thione;

12-H-6,7-dihydro-7-methyl-12-ethyl-pyrido[2,3-b]pyrido-[2',3'-4,5] thien[2,3-f]-[1,4]diazepin-6-thione;

12-H-7-methyl-12-ethyl-5a,6,7,12a-tetrahydro-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one (5a, 12a, cis);

12-H-7-benzyl-12-ethyl-5a,6,7,12a-tetrahydro-pyrido[2,3-b]pyrido-[2',3'-4,5]furo[2,3-f]-[1,4]diazepin-6-one (5a, 12a, cis);

12-H-5,6-dihydro-5-methyl-indole[3,2-b]pyrido[3,2-f][1,5]diazepin-6-one;

12-H-5,6-dihydro-5-methyl-12-acetyl-indole[3,2-b]pyrido[3,2-f]-[1,5]diazepin-6-one;

12-H-5,6-dihydro-10-chloro-5-methyl-indole[3,2-b]pyrido[3,2-f]-[1,5]diazepin-6-one;

12-H-5,6-dihydro-12-acetyl-10-chloro-5-methyl-indole[3,2-b]pyrido [3,2-f]-[1,5]diazepin-6-one;

12-H-5,6-dihydro-5-methyl-7,12-diethyl-indole[3,2-b]pyrido[3,2-f][1,5]diazepin-6-one;

12-H-5,6-dihydro-7-ethyl-5-methyl-10-chloro-indole[3,2-b]pyrido [3,2-f]-[1,5] diazepin-6-one;

12-H-5,6-dihydro-1,2,8,9-ethyl-5-methyl-10-chloro-indole[3,2-b] pyrido[3,2-f]-[1,5]diazepin-6-one;

1-ethyl-6,8,9-trimethyl-1,6-dihydro-pyrido[2,3-f][2,1,5]benzothio-diazepin-5,5-dioxide;

12-H-5,6-dihydro-5-methyl-12-ethyl-benzofuro[3,2-b]pyrido[3,2-

f] [1,5]-diazepin-6-one;

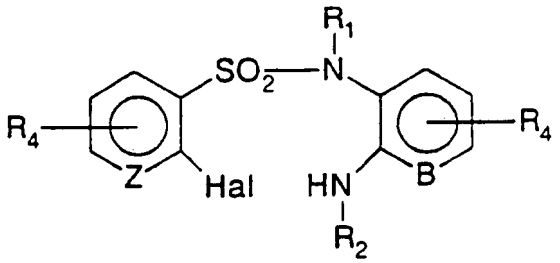
12-H-6,7-dihydro-7-methyl-12-isopropyl-pyrido[2,3-b]-pyrido-[2',3'-4,5]furo[2,3-f][1,4]diazepin-6-one;

12-H-6,7 dihydro-7-methyl-12-isopropyl-pyrido[2,3-b]pyrido[2',3'-4,5]thien[2,3-f][1,4]diazepin-6-one;

12-H-6,7-dihydro-7-methyl-12-isopropyl-pyrido-[2,3-b]-pyrido-[2',3'-4,5]furo[2,3-f][1,4]diazepin-6-thione;

12-H-6,7-dihydro-7-methyl-12-isopropyl-pyrido-[2,3-b]pyrido[2',3'-4,5]thien[2,3-f][1,4]diazepin-6-thione.

4. A compound of formula (II)



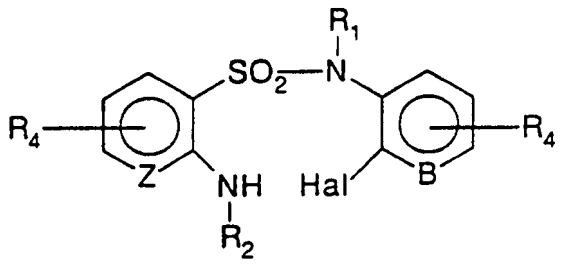
(II)

wherein : Z represents a nitrogen group, optionally substituted with R_2 group; or with $=C-R_5$ wherein R_5 is selected from the group consisting of hydrogen , alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl, hydroxy, amino or acetamino , nitro , a cyano or an azido group;

R_1 and R_2 equal or different from each other, are selected from the group consisting of hydrogen, alkyl or fluoroalkyl of from 1 to 6 carbon atoms, cycloalkyl of from 3 to 5 carbon atoms, alkenyl or

an alkinyl of from 3 to 5 carbon atoms, an alkoxy-alkyl of from 2 to 6 carbon atoms, benzyl, C_{2-6} alkylacyl, phenylacyl wherein the phenyl group is optionally substituted with a group selected from NO_2, CN, halogen; R_4 is selected from the group consisting of hydrogen, alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl , a hydroxy , amino or acetamino, a nitro, cyano and azido group, B is N or $=C-R_5$, wherein R_5 is selected from the group consisting of hydrogen , alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl , hydroxy amino or acetamino group, nitro, cyano and azido group, Hal is a halogen atom.

5. A compound of formula (III)

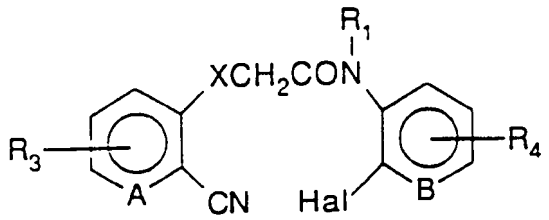


(III)

wherein : Z represents a nitrogen group, optionally substituted with R_2 group; or with $=C-R_5$ wherein R_5 is selected from the group consisting of hydrogen , alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl, hydroxy, amino or acetamino , nitro , a cyano or an azido group;

R_1 and R_2 equal or different from each other, are selected from the group consisting of hydrogen, alkyl or fluoroalkyl of from 1 to 6 carbon atoms, cycloalkyl of from 3 to 5 carbon atoms, alkenyl or an alkinyl of from 3 to 5 carbon atoms, an alkoxy-alkyl of from 2 to 6 carbon atoms, benzyl, C_{2-6} alkylacyl, phenylacyl wherein the phenyl group is optionally substituted with a group selected from NO_2, CN, halogen; R_4 is selected from the group consisting of hydrogen, alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl , a hydroxy , amino or acetamino, a nitro, cyano and azido group, B is N or $=C-R_5$, wherein R_5 is selected from the group consisting of hydrogen , alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl , hydroxy amino or acetamino group, nitro, cyano and azido group, Hal is a halogen atom.

6. A compound of formula (VI)



(VI)

wherein A represents a nitrogen atom or $=C-R_5$, wherein R_5 is selected from the group consisting of hydrogen , alkyl of from 1

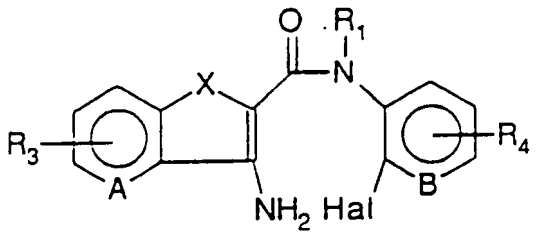
to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl , hydroxy amino or acetamino group, nitro, cyano and azido group;

B has the same meaning as A, but it cannot be equal to $=C-R_5$ when A = $=C-R_5$,

X = =CH, $=CR_6$, O, S, NR_7;

R_1 is selected from the group consisting of hydrogen, alkyl or fluoroalkyl of from 1 to 6 carbon atoms, cycloalkyl of from 3 to 5 carbon atoms, alkenyl or an alkinyl of from 3 to 5 carbon atoms, an alkoxy-alkyl of from 2 to 6 carbon atoms, benzyl, C_{2-6} alkylacyl, phenylacyl wherein the phenyl group is optionally substituted with a group selected from NO_2, CN, halogen; R_3 and R_4 equal or different from eachother are selected from the group consisting of hydrogen, alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl , a hydroxy , amino or acetamino, a nitro, cyano and azido group, Hal is a halogen atom.

7. A compound of formula (VII)



(VII)

wherein A represents a nitrogen atom or $=C-R_5$, wherein R_5 is

selected from the group consisting of hydrogen , alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl , hydroxy amino or acetamino group, nitro, cyano and azido group;

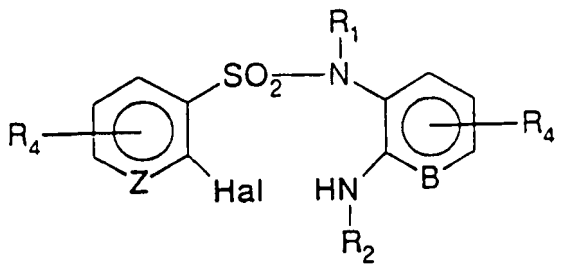
B has the same meaning as A, but it cannot be equal to $=C-R_5$ when A = $=C-R_5$,

X = =CH, $=CR_6$, O, S, NR_7;

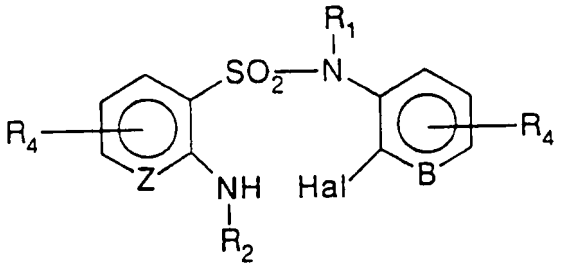
R_1 is selected from the group consisting of hydrogen, alkyl or fluoroalkyl of from 1 to 6 carbon atoms, cycloalkyl of from 3 to 5 carbon atoms, alkenyl or an alkinyl of from 3 to 5 carbon atoms, an alkoxy-alkyl of from 2 to 6 carbon atoms, benzyl, C_{2-6} alkylacyl, phenylacyl wherein the phenyl group is optionally substituted with a group selected from NO_2, CN, halogen; R_3 and R_4 equal or different from eachother are selected from the group consisting of hydrogen, alkyl of from 1 to 3 carbon atoms, hydroxyalkyl of from 1 to 3 carbon atoms, alkoxy of from 1 to 3 carbon atoms, halogen, trihalomethyl , a hydroxy , amino or acetamino, a nitro, cyano and azido group, Hal is a halogen atom.

8. A process for preparing the compound of formula (I) as claimed in claim 1 wherein n = 1 and W = SO_2 comprising the following steps:

a) reacting the sulfonamides of general formula (II) or (III)



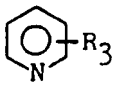
(II)

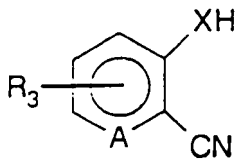


(III)

wherein R_4, R_5, Z and B have been previously defined for the compounds of formula (I); R_1 and R_2 have the same meanings of the corresponding substituents of the compounds of formula (I) or represent a protecting group as for example acetyl, benzoyl, benzyl, Hal represents a halogen atom, preferably chlorine or bromine, in an organic solvent in the presence of a base and optionally of copper or its salts in a catalytic amount at temperatures comprised between 60 ° - 200 °C.

b) optionally alkylating the compound obtained in step (a)with R_2M.

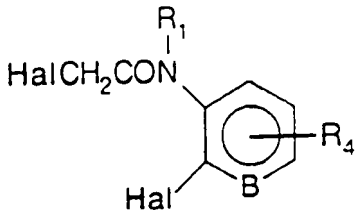
9. A process for preparing the compound of formula (I) as claimed in claim 1 wherein n = 0, W = C=O or C=S, X=O, S or NR_7, R_8 and R_9 form a ring  wherein A represent a nitrogen atom or a =C-R_5 group wherein R_7, R_3 and R_5 have the above mentioned meanings, comprising condensing the compound of general formula (IV) :



(IV)

wherein , R_3 and A have the above mentioned meanings, with the

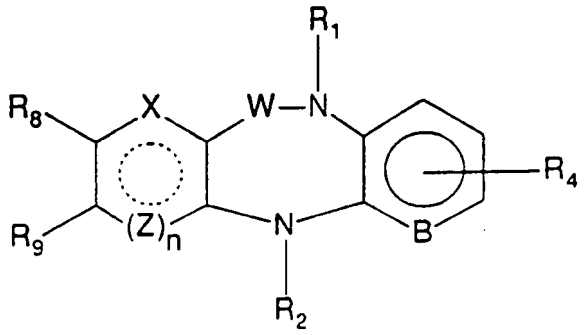
compound of formula (V):



(V)

wherein Hal, B and R_4 have the above mentioned meanings, thereby obtaining the compound of formula (VI), which is then cyclized to the compound of formula (I) having R_2 = H and W =C=O, optionally alkylated on the Nitrogen atom with R_2M and it is optionally sulphurated.

10. Use of the compounds of formula (I)



(I)

wherein :

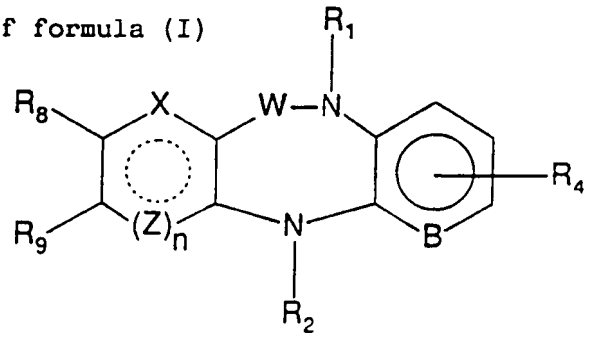
i') n = 0, X = O, W = C=O, B= N, R_1 =CH_3, R_8 and R_9 form a benzenic ring and R_2 is H,

or

ii') n = 1, W =SO_2, X= B = Z = CH for the preparation of pharmaceutical compositions having antiviral activity in a suitable form for the oral or parenteral administration.

11. A therapeutic method for the treatment of viral diseases,

comprising orally or parenterally administering to a host in need of said treatment a therapeutically effective amount of the compound of formula (I)



(I)

wherein :

i') n = 0, X = O, W = C=O, B= N, R_1 =CH_3, R_8 and R_9 form a benzenic ring and R_2 is H,

or

ii') n = 1, W =SO_2, X= Z = B = CH for the preparation of pharmaceutical compositions having antiviral activity in a suitable form for the oral or parenteral administration.

12. A pharmaceutical composition having antiviral activity comprising as the active principle a therapeutically effective amount of at least one compound according to claim 1, and its pharmaceutically acceptable salts in combination with suitable excipients and optionally in the presence o other antiviral agents.

13. The pharmaceutical composition as claimed in claim 12 in a suitable form for the oral or parenteral administration.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/00102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D513/04 C07D513/14 C07D491/22 C07D495/22 C07D491/14
C07D471/14 C07D213/76 C07D213/84 C07D495/04 /
/(C07D513/04,285:00,221:00),(C07D513/14,285:00,221:00,221:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,5 087 625 (K.D. HARGRAVE ET AL.) 11 February 1992 see claim 1 ---	1,12
X	EP,A,0 393 530 (BOEHRINGER) 24 October 1990 see claim 1 ---	1,12
X	EP,A,0 393 604 (BOEHRINGER) 24 October 1990 cited in the application see claims 1,8 ---	1,12
X	EP,A,0 429 987 (BOEHRINGER) 5 June 1991 see claims 1,15 --- -/--	1,12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 1994	- 3. 06. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/00102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 (C07D491/22,307:00,243:00,221:00,221:00),(C07D495/22,333:00, 243:00,221:00,221:00),(C07D491/14,307:00,243:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF HETEROCYCLIC CHEMISTRY vol. 27 , 1990 , PROVO US pages 1369 - 1375 G. VITI ET AL. 'Synthesis of new arylbenzofurodiazepin-6-ones' see page 1370, compound 3f; page 1372, compounds 5b,5e; page 1373, compounds 2c, 2f ---	1,6,7
X	JOURNAL OF MEDICINAL CHEMISTRY vol. 34, no. 4 , 1991 , WASHINGTON US pages 1356 - 1362 D. GIANNOTTI ET AL. 'New dibenzothiadiazepine derivatives with antidepressant activities' see page 1361, compound 4j --- -/--	5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 May 1994	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Alfaro Faus, I

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	JOURNAL OF ORGANIC CHEMISTRY vol. 37, no. 6 , 1972 , EASTON US pages 854 - 859 F.A. DAVIS ET AL. 'Chemistry of the sulphur-nitrogen bond. II. A mechanistic study of the rearrangement of 2-nitrobenzenesulfenanilides to 2-aminobenzenesulfonanilides' see page 858, compound 5d ---	5
X	CHEMICAL ABSTRACTS, vol. 88, no. 9, 1978, Columbus, Ohio, US; abstract no. 62092g, PILLAI, N.V. RAJASEKHARAN 'Photorearrangement of bis(2-nitrophenyl) disulfide in the presence of aromatic amines to 2-aminobenzenesulfonanilides' page 359 ; see abstract & CHEM. IND. 1977, (15), 665-6 ---	5
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X	GB,A,948 833 (BAYER) 5 February 1964 see page 4, line 39 - line 41 ---	5
X	EP,A,0 268 990 (FUJISAWA) 1 June 1988 see page 20, line 12 - line 15 ---	5
X	GB,A,1 360 365 (RHONE-POULENC) 17 July 1974 see page 1, lines 24 - 26, formula V, claim 13 -----	4

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 94/00102

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-1360365		US-A- 3868382	25-02-75